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<p>(21) International Application Number: PCT/US99/26353 (22) International Filing Date: 8 November 1999 (08.11.99) (30) Priority Data: 60/107,680 9 November 1998 (09.11.98) US (71) Applicant (for all designated States except US): AXYS PHARMACEUTICALS, INC. [US/US]; 180 Kimball Way, South San Francisco, CA 94080 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DENER, Jeffrey, Mark [US/US]; 1948 Vista Cay, San Mateo, CA 94404-2412 (US). LY, Cuong, Quoc [US/US]; Apartment #4, 251 Collins Street, San Francisco, CA 94118 (US). (74) Agents: KATHARDEKAR, Vinit, G. et al.; Axys Pharmaceuticals, Inc., 180 Kimball Way, South San Francisco, CA 94080 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: PROCESS FOR THE SYNTHESIS OF QUINAZOLINONES</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div data-bbox="436 1167 769 1325"> <p>(1 A)</p> </div> <div data-bbox="852 1167 1218 1293"> <p>(1 B)</p> </div> </div> <p>(57) Abstract</p> <p>The present invention provides a process for synthesizing a compound or a library of compounds of Formula (1A) and (1B).</p>		

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PROCESS FOR THE SYNTHESIS OF QUINAZOLINONES

FIELD OF INVENTION

5 The present invention relates to a process for the synthesis of Quinazolinones having potential biological activity.

BACKGROUND OF THE INVENTION

10 A variety of substituted quinazolinones have been reported in the literature. These Quinazolinones are known to be biologically active. One such class of Quinazolinones is 2,3-dihydro-4(1H)-quinazolinones. It has been reported that these Quinazolinone compounds were studied for their pharmacodynamic, insecticidal, and antifungal activity.

15 Other studies, for example as reported by Yale and Kalkstein in J. Med. Chem. 10(3), 334-336, suggest that the 2,3-Dihydro-4(1H)-Quinazolinones were effective inhibitors of multiplication of the Earle's L cell line. Quinazolinone derivatives were also shown to act as cholerectic agents useful in the treatment of cholelithiasis and jaundice, as reported by Okuura
20 et. al. in J. Med. Chem., 1972, Vol. 15, No. 5, 518-532. It has also been reported by Ozaki et. al. in J. Med. Chem., 1985, 28, 568-576, that the 4(1H)-Quinazolinones were studied as potent antiinflammatory agents.

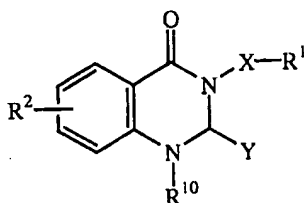
 Given the wide spread utility of the Quinazolinone compounds, there is a continuing need to synthesize Quinazolinone compounds. Traditional
25 synthetic methods are time consuming and can only make these compounds on an individual basis. There is thus a need for a synthetic process which will

produce a large number (library) of such Quinazolinone compounds in a rapid manner.

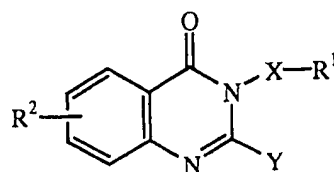
SUMMARY OF THE INVENTION

5

The present invention provides a process for synthesizing a compound or a library of compounds represented by Formula 1A and 1B:



Formula 1A



Formula 1B

10

wherein:

R¹ is selected from a group consisting of -C₁₋₁₀ alkyl, -OC₁₋₄ alkyl, -C₄₋₁₀ saturated or partially unsaturated cyclo alkyl, heteroaryl, aryl substituted with
 15 R³, R⁴, and R⁵, and -C₁₋₄ alkyl substituted with one or more of aryl or heteroaryl;

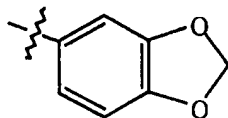
R² is selected from H, -C₁₋₄ alkyl, -COOH, -COOC₁₋₄ alkyl, -NO₂, -NH₂, -C₁₋₈ alkyl-C(O)-NH₂, -NHC₁₋₈ alkyl, aryl-C(O)-NH₂, -CN, -O-C₁₋₄ alkyl, and halogen;

X represents -(CH₂)₁₋₄;

20 Y represents -C₁₋₆ alkyl, -C₄₋₁₀ cycloalkyl, or aryl substituted with R⁶, R⁷, and R⁸; R³, R⁴, and R⁵ independently at each occurrence represent H, -CF₃, -OCF₃, halogen, -OC₁₋₄ alkyl or -C₁₋₆ alkyl;

R⁶, R⁷, and R⁸ independently at each occurrence represent H, -O-C₁₋₄ alkyl, alkyl, -O-Ph-O-alkyl, -O-Ph-alkyl, -Ph, halogen, or -CN; alternatively

25 when R⁶ and R⁷ along with the phenyl ring to which they are attached represent



R^8 is H; and

R^{10} represents H, C_1 - C_4 alkyl, benzyl, substituted benzyl, C_2 - C_6 alkenylene,

5 substituted alkyl, or $-(CH_2)_{1,3}-COOC_{1,4}$ alkyl;

said process comprising the steps of:

(i) reacting an aldehyde of Formula A

$Y-CHO$ Formula A,

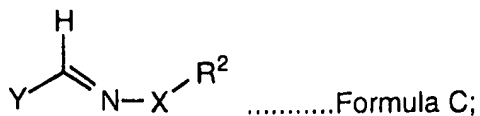
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with an amine of Formula B

R^2-X-NH_2 Formula B,

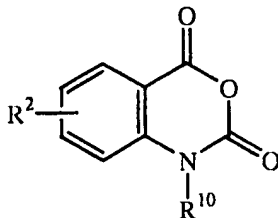
wherein R^2 , X, and Y are as defined above,

15 to yield a compound of Formula C



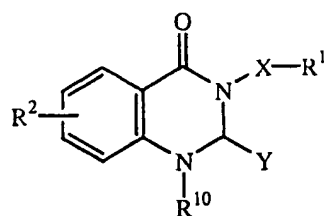
(ii) reacting the compound of Formula C with a compound of Formula D

20



.....Formula D,

to yield a compound of Formula 1A



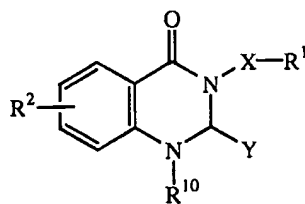
.....Formula 1A

where R^1 , R^2 , R^{10} and Y are as defined above; and

- (iii) optionally oxidizing a compound of Formula 1A, when R^{10} is H, followed
 5 by treating with an aminomethyl polystyrene resin, to yield a compound of
 Formula 1B.

Another aspect of the present invention provides a process for
 synthesizing a compound or a library of compounds represented by Formula
 1A:

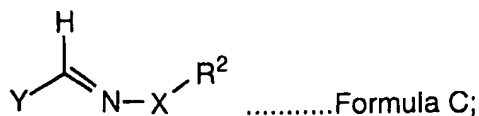
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Formula 1A

wherein X , Y , R^1 , R^2 and R^{10} are as defined above,
 said process comprising:

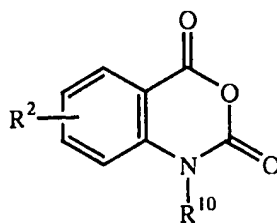
- 15 reacting a compound of Formula C



.....Formula C;

with a compound of Formula D

20

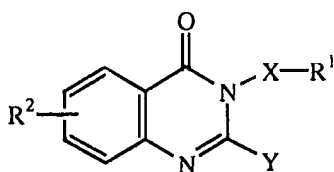


.....Formula D,

followed by optional treatment with an aminoalkyl, preferably aminomethyl, polystyrene resin to yield a compound of Formula 1A.

5

In yet another aspect of the present invention is provided a process for synthesizing of a compound or a library of compounds of Formula 1B



Formula 1B

10

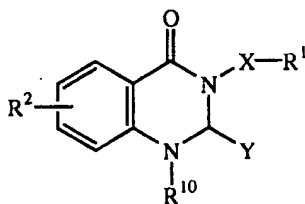
wherein:

R¹, R², X, Y, are as defined above, and R¹⁰ represents H,

said process comprising:

oxidizing a compound of Formula 1A,

15



Formula 1A

followed by treating with an aminomethyl polystyrene resin, to yield a compound of Formula 1B.

DETAILED DESCRIPTION OF THE INVENTION

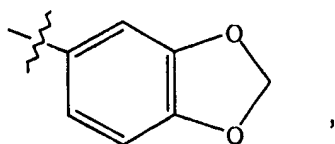
Step (i) of the process of the present invention may be performed
5 successfully using either solutions or suspensions of the aldehyde of Formula
A or the amine of Formula B. However preferred embodiments of the present
invention provide a process wherein step (i) comprises using solutions of the
aldehyde of Formula A, and the amine of Formula B. Illustrative examples of
solvents which may be used to prepare the solutions of the aldehyde of
10 Formula A and the amines of Formula B are acids, protic solvents, and polar
solvents. Preferred acid solvents are acetic acid, and propionic acid.
Preferred protic solvents are methanol and ethanol. Preferred polar solvents
are DMF, DMSO, and dioxane. A further preferred embodiment provides a
process wherein step (i) comprises using at least one of an acetic acid, or a
15 propionic acid solution of the aldehyde of Formula A and the amine of
Formula B. The foregoing signifies that the process of the preferred
embodiment comprises at least a solution of the aldehyde and the amine in
acetic acid or propionic acid, but can comprise a mixture of the two with or
without additional solvents.

20 Another preferred embodiment provides a process wherein step (ii)
comprises reacting an acetic acid solution of a compound of Formula C with a
solution of a compound of Formula D. Preferably the solution of a compound
of Formula D is prepared using at least one solvent selected from the group
consisting of DMF, DMSO, dioxane, methylene chloride, acetic acid,
25 chloroform, THF, and propionic acid. Particularly preferred solvents for
preparing the solution of a compound of Formula D are at least one of acetic
acid, methylene chloride, THF, and DMF.

Yet another preferred embodiment provides a process wherein step (iii)
comprises oxidizing a compound of Formula 1A using iodine, KMnO_4 , or
30 DDQ/CHCl_3 suspension. Also provided in another preferred embodiment of
the present invention is a process wherein R' is selected from a group

consisting of $-C_{1-6}$ alkyl, $-OC_{1-4}$ alkyl, $-C_{4-6}$ saturated or partially unsaturated cyclo alkyl, heteroaryl, aryl substituted with R^3 , R^4 , and R^5 , or $-C_{1-4}$ alkyl substituted with one or more of aryl or heteroaryl; R^2 is selected from H, $-C_{1-4}$ alkyl, $-O-C_{1-4}$ alkyl, and halogen; Y represents $-C_{1-4}$ alkyl, or aryl substituted with R^6 , R^7 , and R^8 ; R^3 , R^4 , and R^5 independently at each occurrence represent H, $-O-C_{1-4}$ alkyl, $-CF_3$, halogen, or $-C_{1-4}$ alkyl; R^6 , R^7 , and R^8 independently at each occurrence represent H, $-O-C_{1-4}$ alkyl, $-C_{1-4}$ alkyl, $-O-Ph$, $-O-C_{1-4}$ alkyl, $-Ph$, or halogen; or when R^6 and R^7 along with the phenyl ring to which they are attached represent

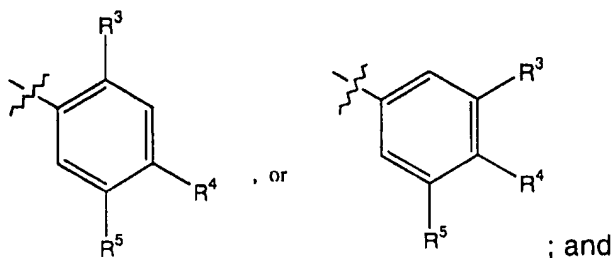
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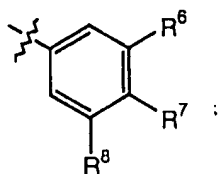
R^8 is H; and R^{10} represents $-C_{1-2}$ alkyl, $-C_{1-2}-Ph$ or $-CH_2-COO-C_2H_5$.

A further preferred embodiment of the present invention provides a process wherein R^1 represents

15



Y represents



20 wherein R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are as defined in the summary of the invention.

Another aspect of the present invention provides a library of compounds synthesized by the processes of the present invention.

EXPERIMENTAL DETAILS

5

General Comments

Both the amines (compounds of Formula B) and aldehydes (compounds of Formula A) are dissolved in acetic acid at a concentration of 0.40 molar and mixed for 1.5-2 hours to allow for imine formation. Next a 10 0.10 molar solution or suspension of the isatoic anhydride (Formula D) in THF is added and the mixture is heated to about 95°-100°C in a block heater for 4 hours. Several oxidation conditions are validated for the final oxidation step, e.g., KMnO_4 /acetone/RT, I_2/CHCl_3 /RT, DDQ/dioxane/RT, etc., but the preferred conditions are DDQ/ CHCl_3 /RT. It was surprisingly found that 15 purification with aminomethyl polystyrene resin removes any unreacted isatoic anhydride, aldehyde, DDQ by-products along with colored impurities, to yield a purer Formula 1B compound.

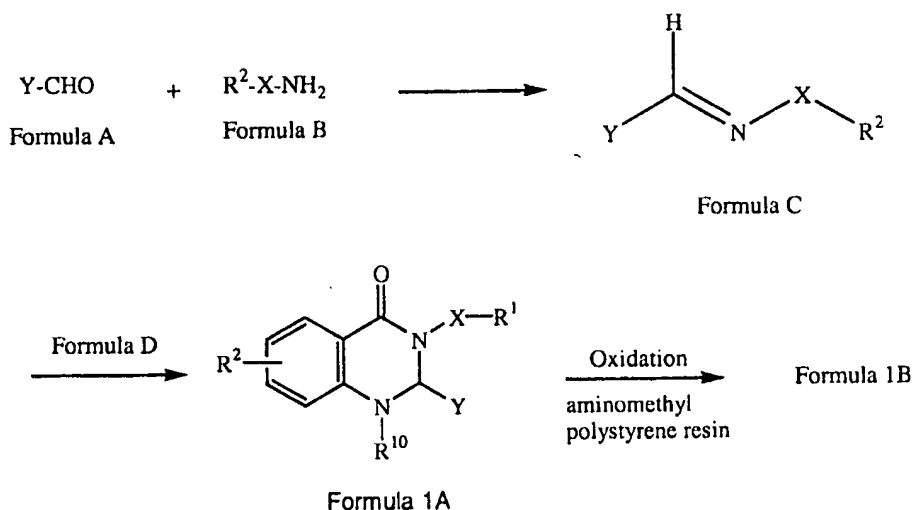
Amines (Compounds of Formula B), and aldehydes (Compounds of Formula A) are commercially available. DDQ reagent was obtained from 20 Aldrich. The 1.20 mmol/g loading, 100-200 mesh aminomethyl polystyrene resin was obtained from Midwest Bio-Tech Incorporated.

The following synthetic scheme (Scheme I) generally describes one of the processes of the present invention.

25

30

Scheme I



5 General Description:

The general process for the synthesis of compounds of Formula 1B is as follows:

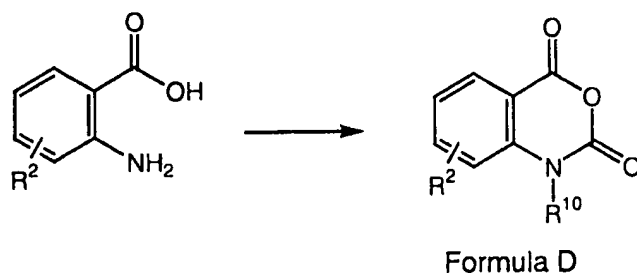
- Step A: Imine (Compound of Formula C) formation: 125 μL of a 0.40 molar solution of the amine (AM, Formula B) in acetic acid (AcOH) was added to a reaction vessel, to which was then added 1 mole equivalent of an aldehyde of Formula A, in acetic acid. This reaction mixture was mixed for about 2 h to yield an imine, a compound of Formula C.
- Cyclization of the imines (Compound of Formula C) with isatoic anhydride: To a solution of the imine in acetic acid was added isatoic anhydride (ISA, compound of Formula D) as a THF solution. The resulting reaction mixture was heated under reduced pressure at a temperature of about 100°C , for up to 6 hours. The reaction mixture was cooled to room temperature to yield a compound of Formula 1A.

DDQ oxidation and aminomethyl polystyrene resin-mediated purification: A compound of Formula 1A was treated with DDQ/ CHCl_3 suspension. This reaction mixture was mixed for up to 6 hours to yield a crude mixture of a compound of Formula 1B.

5 Compounds of Formula 1B were purified by further treatment with aminomethyl polystyrene resin. The reaction mixture comprising a compound of Formula 1B was transferred to another reaction vessel containing aminomethyl polystyrene resin. This mixture was shaken for up to 24 hours. The resin solution was then filtered through silica gel. The silica
10 gel was washed with chloroform. The combined organic solvents were combined, evaporated to yield a compound of Formula 1B.

Isatoic anhydrides (compounds of Formula D) were prepared as shown in the following reaction Scheme II.

15 Scheme II



20 where R^2 and R^{10} are as defined in the summary of the invention.

Isatoic anhydrides, compounds of Formula D, were prepared, as outlined in Scheme II, by treatment of the corresponding commercially available anthranillic acids with phosgene in an inert solvent, preferably toluene. Procedures for the specific isatoic anhydrides syntheses are given
25 below.

5-Methoxyisatoic Anhydride

To a mixture of 10.0g (60.0 mmol) of 5-methoxyanthranilic acid in 80 mL of 1,4-dioxane was slowly added 100 mL (193 mmol) of a 1.93 molar solution of phosgene, or thiophosgene in an inert solvent, preferably a hydrocarbon solvent such as toluene, at room temperature. The mixture was stirred overnight at room temperature. This mixture was then concentrated in vacuo to a small volume. This concentrated reaction mixture was filtered through silica and the filter cake was washed with hexane to give 10.99g (95.2%) of the 5-methoxyisatoic anhydride as an off white solid. MS (CI mode) m/z 176 (M-18, 100%), 194 (M+H, 71%).

5-Methylisatoic Anhydride:

To a mixture of 10.0g (66.0 mmol) of 5-methylanthranilic acid in 60 mL of 1,4-dioxane was slowly added 100 mL (193 mmol) of a 1.93 molar solution of phosgene in toluene, at room temperature. The mixture was stirred overnight at room temperature, followed by concentration in vacuo to a small volume. The concentrated reaction mixture was filtered through silica and the filter cake was washed with hexane to give 9.81g (83.7%) of the 5-methylisatoic anhydride as a light yellow solid. MS (CI mode) m/z 160 (M-18, 100%), 178 (M+H, 71%).

3-Methylisatoic Anhydride: To a mixture of 10.0g (66.0 mmol) of 3-methylanthranilic acid in 60 mL of 1,4-dioxane was slowly added 100 mL (193 mmol) of a 1.93 molar solution of phosgene in toluene, at room temperature. The mixture was stirred overnight. The mixture was concentrated in vacuo to yield a residue which was triturated with ethyl acetate-hexane (1:4), filtered, washed with hexane and dried to afford 11.66g (99.5%) of the 3-methylisatoic anhydride as an off white solid. MS (CI mode) m/z 160 (M-18, 100%), 178 (M+H, 90%).

5-Chloro-N-methyl Isatoic anhydride:

To a stirred solution of 4.95g (25.1 mmol) of 5-chloroisatoic anhydride in 80 mL of dry N,N-dimethylformamide (DMF) was added 5.15g (48.6 mmol) of powdered sodium carbonate forming a suspension. The suspension was then treated with 2.00 mL (4.86g; 32.1 mmol) of iodomethane. The resulting suspension was stirred for 13 hours, then it was poured into 300 mL of water with vigorous stirring. After 2-3 minutes the resulting precipitate was filtered, and washed with 200 mL of water. The filter cake was dissolved in 200 mL of dichloromethane and this solution was dried (Na_2SO_4). The solution was concentrated in vacuo and the residue triturated with ethyl acetate-hexane (1:3). The solid was filtered, washed with ethyl acetate-hexane (1:3), and finally hexane. The solid was dried in vacuo to give 3.90g (73%) of the title compound as a pale yellow solid. ^1H NMR (300 MHz, DMSO- D_6) δ 3.42 (s, 3H), 7.44 (d, 1H), 7.85 (d, 1H), 7.83 (d, 1H), 7.92 (d, 1H). MS (CI Mode) m/z 212 (M+H, 100%), 240 (M+29, 8%). HPLC analysis showed a single peak.

N-Benzylisatoic Anhydride:

A solution of 5.00g (22.0 mmol) of N-benzyl anthranillic acid in 30 mL of 1,4-dioxane was briefly cooled in an ice water bath, then 60 mL (116 mmol) of a 1.93 molar solution of phosgene in toluene was added. The solution was stirred for 2 minutes in the ice bath, then it was stirred for 5 hours at room temperature. Nitrogen gas was then passed through the solution for 30 minutes then the reaction mixture was concentrated in vacuo. The residue was dried under high vacuum to give 5.62g (100%) of N-benzylisatoic anhydride as an off-white solid. ^1H -NMR (300 MHz, DMSO- D_6) δ 5.25 (s, 5H), 7.18-7.39 (m, 7H), 7.69 (t, 1H), 7.99 (d, 1H). MS (CI Mode) m/z 254 (M+H, 100%), 282 (M+29, 11%). HPLC analysis showed a single peak.

4-Chloroisatoic Anhydride:

To a mixture of 10.0g (58.0 mmol) of 4-chloroanthranilic acid in 100 mL of 1,4-dioxane was slowly added 100 mL (193 mmol) of a 1.93 molar solution

of phosgene in toluene, at room temperature. The mixture was stirred overnight. The mixture was concentrated to yield a residue which was triturated with ethyl acetate-hexane (1:4), filtered, washed with hexane and dried to afford 8.78g (76.2%) of the 4-chloroisatoic anhydride as a light brown solid. MS (CI mode) m/z 198 (M+H, 100%), CI pattern 200, 35%.

3-Methoxyisatoic Anhydride:

To a mixture of 10.0g (60.0 mmol) of 3-methoxyanthranilic acid in 60 mL of 1,4-dioxane was slowly added 100 mL (193 mmol) of a 1.93 molar solution of phosgene in toluene, at room temperature. The mixture was stirred overnight. The mixture was concentrated to yield a residue which was triturated with ethyl acetate-hexane (1:4), filtered, washed with hexane and dried to afford 11.33g (98%) of the 3-methoxyisatoic anhydride as an off white solid. MS (CI mode) m/z 176 (M-18, 100%), 194 (M+H, 53%).

6-Methylisatoic Anhydride:

To a mixture of 10.0g (66.0 mmol) of 6-methylanthranilic acid in 60 mL of 1,4-dioxane was slowly added 100 mL (193 mmol) of a 1.93 molar solution of phosgene in toluene, at room temperature. The mixture was stirred overnight. The mixture was concentrated to yield a residue which was triturated with ethyl acetate-hexane (1:4), filtered, washed with hexane and dried to afford 11.57g (98.7%) of the 3-methoxyisatoic anhydride as a light brown solid. MS (CI mode) m/z 160 (M-18, 100%), 178 (M+H, 95%).

4,5-Dimethoxyisatoic Anhydride:

To a mixture of 10.0g (51.0 mmol) of 4,5-dimethoxyanthranilic acid in 80 mL of 1,4-dioxane was slowly added 100 mL (193 mmol) of a 1.93 molar solution of phosgene in toluene, at room temperature. The mixture was stirred overnight. The mixture was concentrated to yield a residue which was triturated with ethyl acetate-hexane (1:4), filtered, washed with hexane and dried to afford 11.0g (97.2%) of the 4,5-dimethoxyisatoic anhydride as a gray solid. MS (CI mode) m/z 206 (M-18, 100%), 224 (M+H, 51%).

The following compounds were prepared using the process of the present invention. The following procedure is representative.

5 **2-[3-(4-methoxyphenoxy)phenyl]-3-(4-trifluoromethylbenzyl)-6-methoxyquinazolin-4-one (Example 6)**

3-(4-methoxyphenoxy)benzylidene-4-trifluoromethylbenzylamine (Compound C)

10 A mixture of 3-(4-methoxyphenoxy)benzaldehyde (0.4 M solution in 125 mL AcOH, 0.5 mmol), and 4-(trifluoromethyl)benzylamine (0.4 M solution in 125 mL AcOH, 0.05 mmol) was shaken at room temperature for 2 hr to yield the subject compound of Formula C.

15 **Dihydro-(2H)-2-[3-(4-methoxyphenoxy)phenyl]-3-(4-trifluoromethylbenzyl)-6-methoxyquinazoline-4-one (Compound E)**

 The 3-(4-methoxyphenoxy)benzylidene-4-trifluoromethylbenzylamine, above, was treated with 500 μ L (0.05mmol) of a 0.10 molar mixture of 5-methoxyisatoic anhydride in THF and heated in a preheated heating block at
20 95°-100°C for 3.5 hr. The solvent evaporated during the heating period, upon cooling the reaction mixture, the subject compound of Formula 1A was obtained.

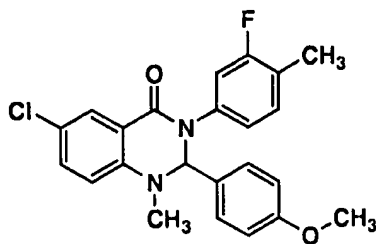
25 **2-[3-(4-methoxyphenoxy)phenyl]-3-(4-trifluoromethylbenzyl)-6-methoxyquinazolin-4-one (Example 6): Compound of Formula 1B**

 The Dihydro-(2H)-2-[3-(4-methoxyphenoxy)phenyl]-3-(4-trifluoromethylbenzyl)-6-methoxyquinazoline-4-one, above, was treated with 1.0 mL (0.05mmol) of 0.05 molar DDQ/ CHCl_3 suspension and the mixture shaken at
30 room temperature for 3.5-4 hr. The oxidation product was then purified by resin capture (with about 80 mg of VHL aminomethyl polystyrene resin) overnight. The reaction flask was covered with Teflon film. The resin solution

was filtered through 30-50 mg of silica gel, washed with 0.5 mL of chloroform. The product was further purified by Prep TLC eluted with 30% ethyl acetate-hexane to give 9.5mg (36.5%) of the subject quinazolin-4-one as a white solid. ¹H-NMR (300 MHz, CDCl₃) δ 3.82 (s, 3H), 3.96 (s, 3H), 5.33 (s, 2H), 6.80-7.73 (m, 15H). MS m/z 533 (M+H, 100%).

Using the above procedures the following compounds of Formula 1A were prepared:

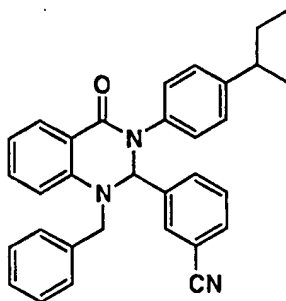
10 Example 1



¹H NMR: (300 MHz, DMSO-*d*₆) δ 2.20 (s, 3H), 2.85 (s, 3H), 3.70 (s, 3H), 6.19 (s, 1H), 6.68 (d, 1H), 6.82 (d, 2H), 6.95 (dd, 1H), 7.05-7.25 (m, 3H), 7.24 (t, 1H), 7.41 (dd, 1H), 7.72 (d, 1H)
MS: (m/z, M+H, 100%): Calc.: 410.12; Obs.: 410.9

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Example 2

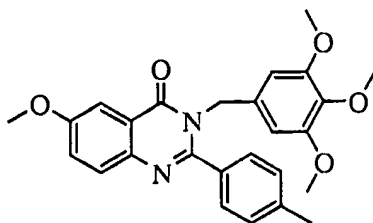


¹H NMR: (300 MHz, DMSO-*d*₆) δ 0.75 (t, 3H), 1.10 (d, 3H), 1.50 (q, 2H), 2.55 (m, 1H), 4.85 (AB q, 2H), 6.47 (s, 1H), 6.78-6.84 (m, 2H), 7.14 (AB q, 4H), 7.20-7.36 (m, 7H), 7.53 (t, 1H), 7.65 (s, 1H), 7.75 (d, 1H), 7.80 (dd, 1H)
MS: (m/z, M+H, 100%): Calc.: 471.23; Obs.: 471.5

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The following compounds of Formula 1B were prepared using the process of the present invention:

Example 3



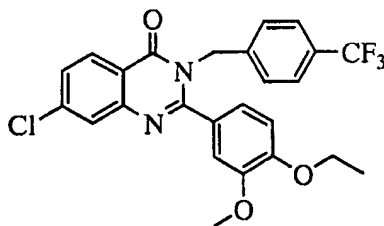
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¹H-NMR (300 MHz, CDCl₃) δ 2.45 (s, 3H), 3.70 (s, 6H), 3.80, (s, 3H), 3.95 (s, 3H), 5.30 (s, 2H), 6.20 (s, 2H), 7.25-7.40 (m, 2H), 7.45 (d, 1H), 7.70-7.80 (m, 2H).

MS (m/z, M+H, 100%): Calc.: 446.18; Obs.: 447.1

15

Example 4

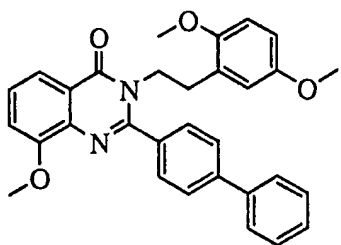


¹H-NMR (300 MHz, CDCl₃) δ 1.55 (t, 3H), 3.60 (s, 3H), 4.10 (q, 2H), 5.40 (s, 2H), 6.70 (d, 1H), 6.90-7.00 (m, 2H), 7.15 (d, 2H), 7.50-7.60 (m, 3H), 7.80 (d, 1H), 8.30 (d, 1H).

MS (m/z, M+H, 100%): Calc.: 488.11 ; Obs.: 489.1.

25

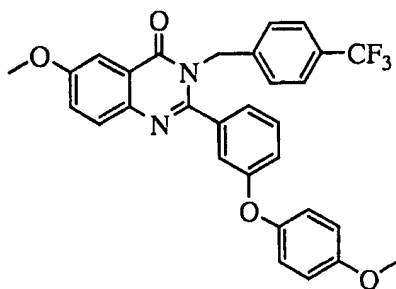
Example 5



5 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 3.00 (t, 2H), 3.40 (s, 3H), 3.65 (s, 3H), 4.00 (s, 3H), 4.40 (t, 2H), 6.45 (d, 1H), 6.60 (d, 1H), 6.70 (dd, 1H), 7.20-7.70 (m, 11H), 8.00 (dd, 1H).

MS (m/z , $M+H$, 100%): Calc.: 492.2; Obs.: 493.2.

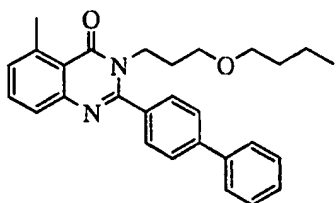
10 Example 6



15 $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 3.82 (s, 3H), 3.96 (s, 3H), 5.33 (s, 2H), 6.73-7.80 (m, 15H).

MS (m/z , $M+H$, 100%): Calc.: 532.16; Obs.: 533.0.

Example 7

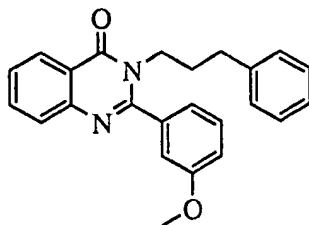


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¹H-NMR (300 MHz, CDCl₃) δ 0.80 (t, 3H), 1.15-1.40 (m, 4H), 1.85-2.00 (m, 2H), 2.90 (s, 3H), 3.15 (t, 2H), 3.40 (t, 2H), 4.40 (br t, 2H), 7.40-7.80 (m, 12H).

MS (m/z, M+H, 100%): Calc.: 426.23; Obs.: 427.1.

10 Example 8

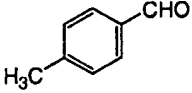
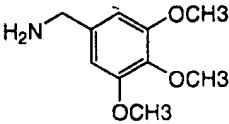
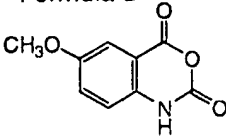
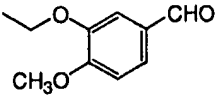
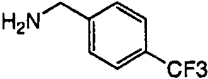
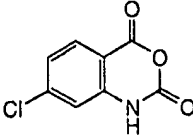
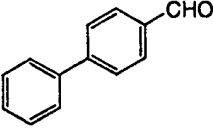
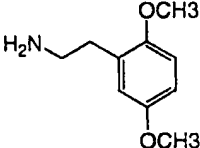
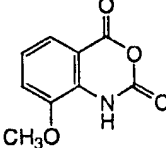
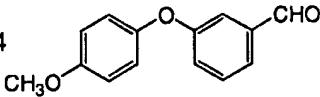
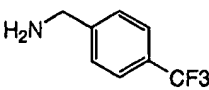
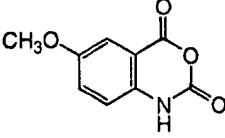
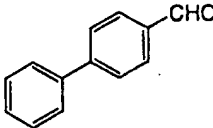
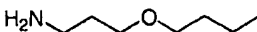
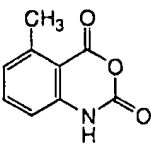
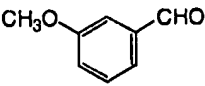
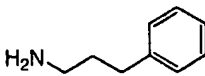
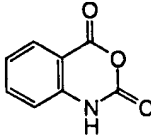


¹H-NMR (300 MHz, CDCl₃) δ 1.95 (br qu, 2H), 2.55 (t, 2H), 3.85 (s, 3H), 4.05 (br t, 2H), 6.95-7.10 (m, 5H), 7.15-7.25 (m, 3H), 7.40 (t, 1H), 7.55 (dt, 1H), 7.70-7.85 (m, 2H), 8.35 (br d, 1H).

MS (m/z, M+H, 100%): Calc.: 370.17; Obs.: 371.1.

20

Starting materials (precursors) for the above six compounds are listed in the following Table 1:

Example	Aldehyde Formula A	Amine Formula B	Isatoic Anhydride Formula D
1			
2			
3			
4			
5			
6			

Chromatography: The above examples were analyzed using a Hewlett Packard HP1100 HPLC employing a Zorbax 4.6 mm x 7.5 cm SP-C18 column with a guard column. Samples were monitored at UV settings of 214 and 254 nm. The column was heated to about 40°C and the flow rate was 0.800 mL per minute for all runs. Gradient elution was performed using water with 0.05% TFA (solvent A) and acetonitrile containing 0.05% TFA (solvent B) as mobile phases. Most samples were prepared as dilute solutions in acetonitrile.

HPLC Gradient

Time (minutes)	% Solvent B
0.00	1.00
5.00	90.0
5.50	100.0
9.00	100.0
10.00	1.00

Mass Spectrometry: Identity of peaks observed by HPLC were determined by electrospray (ESI) LC/MS analysis on a Sciex 150 MCA mass spectrometer with a Shimadzu LC-10 HPLC. Most samples were prepared as dilute solutions in acetonitrile or methanol. Compounds were analyzed by direct injection MS analysis was performed on the Sciex 150 MCA mass spectrometer according to the following conditions:

LC/MS Assay:

Injection volume: 10 mL
Column: Zorbax 3.0 x 50.0 mm column with inline filter
Temperature: 40°C

Gradient:	0-100% B over 6.0 min, 100% B for 1.0 min, 0% B for 2.0 min.
Mobile Phase (Solvent A)	99% water/1% MeOH containing 0.05% AcOH
5 Mobile Phase (Solvent B)	99% MeOH/1% water containing 0.05% AcOH

MS Assay:

10 Mode:	Positive ion ESI
injection volume	10 mL
flow rate	0.3 mL/min, 90% solvent B

DEFINITIONS AND ABBREVIATIONS

15

As used in the present invention the following terms and abbreviations have the following meaning, unless otherwise indicated.

Library of compounds: This term indicates a collection of independent (individual) compounds that are synthesized by the process of the present invention. Generally the term library of compounds indicates a collection of individual compounds distinct from one another. Also included in the library of compounds is a mixture of the individual compounds.

"Alkyl", or "alkyl radical" is meant to indicate a hydrocarbon moiety of up to 8 carbon atoms, unless indicated otherwise. This hydrocarbon can be saturated or unsaturated, is generally attached to at least one other atom, and can be straight chain, or branched, or cyclic. The term straight chain alkyl is meant to represent an unbranched hydrocarbon moiety of up to 8 carbon atoms. An example of a straight chain alkyl is a n-pentyl group.

The term "cycloalkyl", "cycloalkyl ring", or "cycloalkyl radical" indicates a saturated or partially unsaturated three to ten carbon monocyclic or bicyclic hydrocarbon moiety which is optionally substituted with an alkyl group.

As used in the present invention, the illustration:



5 generally indicates the point of attachment of the group, comprising the illustration, to another group or atom. The term "protic solvent" represents a solvent that is capable of donating a proton. Illustrative examples are inorganic and organic acids, and alcohols, including methanol, ethanol, propanol, and butanol.

10 The term "Ph" represents an optionally substituted phenyl radical or group. The term "aryl" means an aromatic monocyclic, bicyclic, or a fused polycyclic hydrocarbon radical containing from 6 to 14 carbon atoms or the number indicated. Thus a C₆-C₁₄ aryl group includes phenyl, naphthyl, anthracenyl, etc. The term "heteroaryl" means aryl, as defined above,
 15 containing 5-14 atoms of the number indicated wherein one or more of the carbon atoms is replaced by a hetero atom chosen from N, O, and S. The hetero atoms can exist in their chemically allowed oxidation states. Thus Sulfur (S) can exist as a sulfide, sulfoxide, or sulfone. Illustrative examples of heteroaryl groups are thienyl, furyl, pyrrolyl, indolyl, pyrimidinyl, isoxazolyl, purinyl, imidazolyl, pyridyl, pyrazolyl, quinolyl, and pyrazinyl.
 20

"Optional substituents" for aryl, hetero aryl, and Ph groups are independently selected from a group consisting of H, -NH₂, halogen, -O-C₁₋₄ alkyl, , -NHC₁-C₄ alkyl, , -N(C₁-C₄)₂ alkyl, CF₃, and C₁₋₄ alkyl.

25 "Optional" "or" "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "optionally is substituted with one to three substituents" means that the group referred to may or may not be substituted in order to fall within the scope of the invention.

30 The term "halogen" represents at least one of chlorine, bromine, iodine, and fluorine radicals. "Inert solvent" as used herein represents

solvents which do not react with the reagents dissolved therein. Illustrative examples of inert solvents are tetrahydrofuran (THF), methylene chloride, dichloro methane (DCM), ethyl acetate (EtOAc), dimethyl formamide (DMF), diaoxane, chloroform, and DMSO.

5

Abbreviations:

ACN = Acetonitrile

AcOH = Acetic Acid

CI = Chemical Ionization

10 DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

EI = Electron Impact

ESI = Electrospray Ionization

ISA = Isatoic Anhydride

LC/MS = Liquid Chromatography/Mass Spectroscopy

15 MeOH = Methanol

RT = Room Temperature

THF = Tetrahydrofuran

TFA = Trifluoroacetic Acid

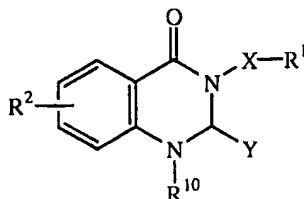
VHL = Very High Load

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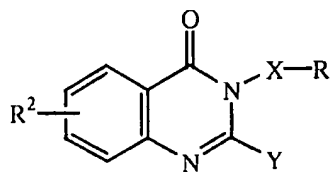
CLAIMS

1. A process for the synthesis of a compound or a library of compounds represented by Formula 1A and 1B:

5



Formula 1A



Formula 1B

wherein:

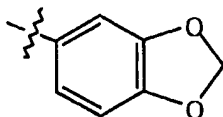
- 10 R¹ is selected from a group consisting of -C₁₋₁₀ alkyl, -OC₁₋₄ alkyl, -C₄₋₁₀ saturated or partially unsaturated cyclo alkyl, heteroaryl, aryl substituted with R³, R⁴, and R⁵, and -C₁₋₄ alkyl substituted with one or more of aryl or heteroaryl;

- R² is selected from H, -C₁₋₄ alkyl, -COOH, -COOC₁₋₄ alkyl, -NO₂, -NH₂, -C₁₋₈ alkyl-C(O)-NH₂, -NHC₁₋₆ alkyl, aryl-C(O)-NH₂, -CN, -O-C₁₋₄ alkyl, and halogen;

- 15 X represents -(CH₂)₁₋₄;

Y represents -C₁₋₆ alkyl, -C₄₋₁₀ cycloalkyl, or aryl substituted with R⁶, R⁷, and R⁸; R³, R⁴, and R⁵ independently at each occurrence represent H, -CF₃, -OCF₃, halogen, -OC₁₋₄ alkyl or -C₁₋₆ alkyl;

- 20 R⁶, R⁷, and R⁸ independently at each occurrence represent H, -O-C₁₋₄ alkyl, alkyl, -O-Ph-O-alkyl, -O-Ph-alkyl, -Ph, halogen, or -CN; alternatively when R⁶ and R⁷ along with the phenyl ring to which they are attached represent



R^8 is H; and

R^{10} represents H, C_1-C_4 alkyl, benzyl, substituted benzyl, C_2-C_6 alkenylene, substituted alkyl, or $-(CH_2)_{1-3}-COOC_{1-4}$ alkyl;

said process comprising the steps of:

- 5 (i) reacting an aldehyde of Formula A



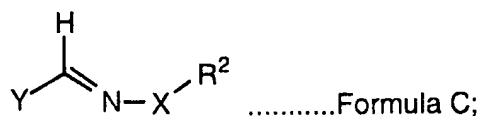
with an amine of Formula B



10

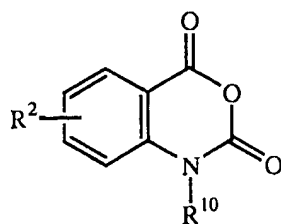
wherein R^2 , X, and Y are as defined above,

to yield a compound of Formula C



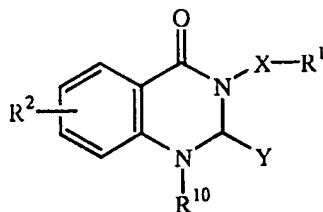
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- (ii) reacting the compound of Formula C with a compound of Formula D



.....Formula D,

- 20 to yield a compound of Formula 1A



.....Formula 1A

where R^1 , R^2 , R^{10} and Y are as defined above; and

- (iii) optionally oxidizing a compound of Formula 1A, when R^{10} is H, followed by treating with an aminomethyl polystyrene resin, to yield a compound of Formula 1B.

2. A process of claim 1 wherein

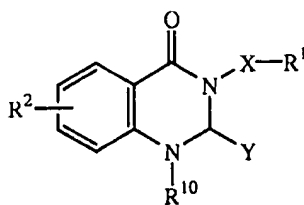
step (i) comprises using acidic or protic solutions of the aldehyde of Formula A and the amine of Formula B;

- step (ii) comprises reacting an acetic acid solution of a compound of Formula C with a solution of a compound of Formula D; and

step (iii) comprises oxidizing a compound of Formula 1A using iodine, $KMnO_4$, or DDQ/ $CHCl_3$ suspension.

3. A library of compounds synthesized by the process of Claim 1.

4. A process for synthesizing a compound or a library of compounds represented by Formula 1A:



Formula 1A

wherein:

- R^1 is selected from a group consisting of $-C_{1-10}$ alkyl, $-OC_{1-4}$ alkyl, $-C_{4-10}$ saturated or partially unsaturated cyclo alkyl, heteroaryl, aryl substituted with R^3 , R^4 , and R^5 , and $-C_{1-4}$ alkyl substituted with one or more of aryl or heteroaryl;

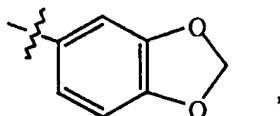
R^2 is selected from H, $-C_{1-4}$ alkyl, $-COOH$, $-COOC_{1-4}$ alkyl, $-NO_2$, $-NH_2$, $-C_{1-8}$ alkyl- $C(O)-NH_2$, $-NHC_{1-6}$ alkyl, aryl- $C(O)-NH_2$, $-CN$, $-O-C_{1-4}$ alkyl, and halogen;
X represents $-(CH_2)_{1-4}-$;

Y represents $-C_{1-6}$ alkyl, $-C_{4-10}$ cycloalkyl, or aryl substituted with R^6 , R^7 , and R^8 ;

5 R^3 , R^4 , and R^5 independently at each occurrence represent H, $-CF_3$, $-OCF_3$, halogen, $-OC_{1-4}$ alkyl or $-C_{1-6}$ alkyl;

R^6 , R^7 , and R^8 independently at each occurrence represent H, $-O-C_{1-4}$ alkyl, alkyl, $-O-Ph-O$ -alkyl, $-O-Ph$ -alkyl, $-Ph$, halogen, or $-CN$; alternatively

when R^6 and R^7 along with the phenyl ring to which they are attached
10 represent

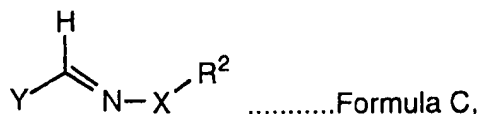


R^8 is H; and

R^{10} represents H, C_1-C_4 alkyl, benzyl, substituted benzyl, C_2-C_6 alkenylene,
15 substituted alkyl, or $-(CH_2)_{1-3}-COOC_{1-4}$ alkyl;

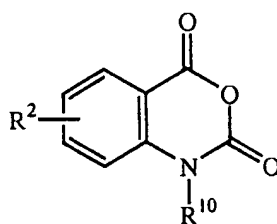
said process comprising:

reacting a compound of Formula C



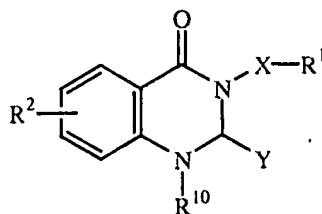
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with a compound of Formula D



.....Formula D,

followed by optional treatment with an aminomethyl polystyrene resin, to yield a compound of Formula 1A



.....Formula 1A

5

where R¹, R², R¹⁰ and Y are as defined above.

5. A process of claim 4 wherein step (ii) comprises reacting an acetic acid solution of a compound of Formula C with a solution of a compound of
10 Formula D.

6. A process of claim 5 wherein the solution of a compound of Formula D is prepared using at least one solvent selected from a group consisting of DMF, DMSO, dioxane, methylene chloride, acetic acid, chloroform, THF, and
15 propionic acid.

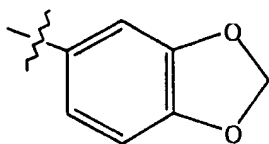
7. A process of claim 6 wherein the solution of a compound of Formula D is prepared using at least one of acetic acid, methylene chloride, THF, and DMF.

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8. A process of claim 7 wherein
R¹ is selected from a group consisting of -C₁₋₆ alkyl, -OC₁₋₄ alkyl, -C₄₋₆ saturated or partially unsaturated cyclo alkyl, heteroaryl, aryl substituted with R³, R⁴, and R⁵, or -C₁₋₄ alkyl substituted with one or more of aryl or heteroaryl;
25 R² is selected from H, -C₁₋₄ alkyl, -O-C₁₋₄ alkyl, and halogen;
Y represents -C₁₋₄ alkyl, or aryl substituted with R⁶, R⁷, and R⁸;
R³, R⁴, and R⁵ independently at each occurrence represent H, -O-C₁₋₄ alkyl, -CF₃, halogen, and -C₁₋₄ alkyl;

R^6 , R^7 , and R^8 independently at each occurrence represent H, $-O-C_{1-4}$ alkyl, $-C_{1-4}$ alkyl, $-O-Ph-O-C_{1-4}$ alkyl, $-Ph$, halogen, or when R^6 and R^7 along with the phenyl ring to which they are attached represent

5

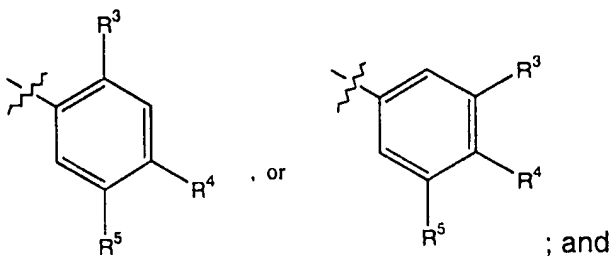


R^8 is H; and

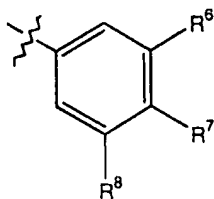
R^{10} represents $-C_{1-2}$ alkyl, $-C_{1-2}-Ph$ or $-CH_2-COO-C_2H_5$.

10 9. A process of claim 8 wherein

R^1 represents



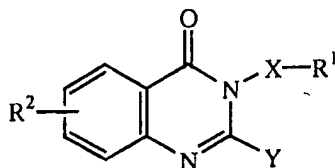
15 Y represents



10. A library of compounds synthesized by the process of Claim 4.

20

11. A process for synthesizing of a compound or a library of compounds of Formula 1B



Formula 1B

5

wherein:

R^1 is selected from a group consisting of $-C_{1-10}$ alkyl, $-OC_{1-4}$ alkyl, $-C_{4-10}$ saturated or partially unsaturated cyclo alkyl, heteroaryl, aryl substituted with R^3 , R^4 , and R^5 , and $-C_{1-4}$ alkyl substituted with one or more of aryl or heteroaryl;

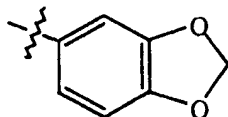
R^2 is selected from H, $-C_{1-4}$ alkyl, $-COOH$, $-COOC_{1-4}$ alkyl, $-NO_2$, $-NH_2$, $-C_{1-8}$ alkyl- $C(O)-NH_2$, $-NHC_{1-6}$ alkyl, aryl- $C(O)-NH_2$, $-CN$, $-O-C_{1-4}$ alkyl, and halogen; X represents $-(CH_2)_{1-4}-$;

Y represents $-C_{1-8}$ alkyl, $-C_{4-10}$ cycloalkyl, or aryl substituted with R^6 , R^7 , and R^8 ;

15 R^3 , R^4 , and R^5 independently at each occurrence represent H, $-CF_3$, $-OCF_3$, halogen, $-OC_{1-4}$ alkyl or $-C_{1-6}$ alkyl;

R^6 , R^7 , and R^8 independently at each occurrence represent H, $-O-C_{1-4}$ alkyl, alkyl, $-O-Ph-O$ -alkyl, $-O-Ph$ -alkyl, $-Ph$, halogen, or $-CN$; alternatively when R^6 and R^7 along with the phenyl ring to which they are attached

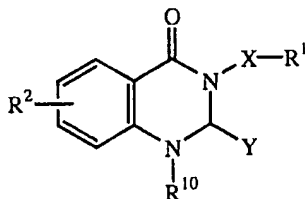
20 represent



R^8 is H; and

R^{10} represents H;

25 said process comprising:
oxidizing a compound of Formula 1A,



Formula 1A

wherein X, Y, R¹, R², and R¹⁰ are as defined above,

followed by treating with an aminomethyl polystyrene resin, to yield a
 5 compound of Formula 1B.

12. A process of claim 11 wherein step (iii) comprises oxidizing a
 compound of Formula 1A using iodine, KMnO₄, or DDQ/CHCl₃ suspension.

10 13. A process of claim 12 wherein

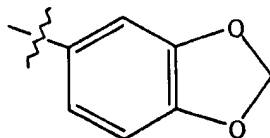
R¹ is selected from a group consisting of -C₁-₆ alkyl, -OC₁-₄ alkyl, -C₄-₆
 saturated or partially unsaturated cyclo alkyl, heteroaryl, aryl substituted with
 R³, R⁴, and R⁵, or -C₁-₄ alkyl substituted with one or more of aryl or heteroaryl;
 R² is selected from H, -C₁-₄ alkyl, -O-C₁-₄ alkyl, and halogen;

15 Y represents -C₁-₄ alkyl, or aryl substituted with R⁶, R⁷, and R⁸;

R³, R⁴, and R⁵ independently at each occurrence represent H, -O-C₁-₄ alkyl, -
 CF₃, halogen, and -C₁-₄ alkyl;

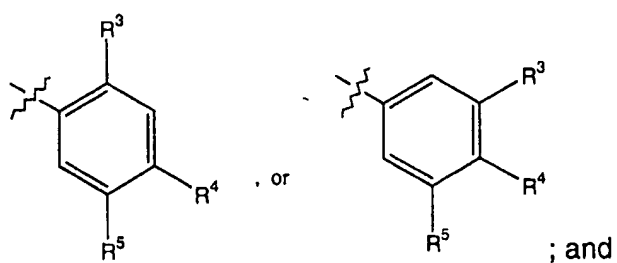
R⁶, R⁷, and R⁸ independently at each occurrence represent H, -O-C₁-₄ alkyl, -
 C₁-₄ alkyl, -O-Ph-O-C₁-₄ alkyl, -Ph, halogen, or

20 when R⁶ and R⁷ along with the phenyl ring to which they are attached
 represent



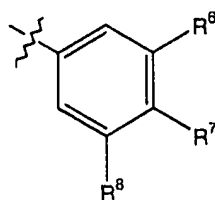
R⁸ is H.

14. A process of claim 13 wherein
R¹ represents



5

Y represents



15. A library of compounds synthesized by the process of Claim 11.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/26353

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 265/12, 239/72

US CL :544/92, 287, 289, 290

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/92, 287, 289, 290

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3,567,746 A (SHETTY) 02 March 1971, col. 11 and 12.	1-15
Y	US 3,761,480 A (SHETTY) 25 September 1973, col. 27.	1-15
A	US 4,710,502 A (WRIGHT, Jr. et. al.) 01 December 1987, col. 1.	1-15
A	US 4,753,944 A (WRIGHT, Jr. et. al.) 28 June 1988, col. 1.	1-15
X	STEIGER, W. et. al. Synthesen von Heterocyclen, 123. Mitt.: Uber Reaktionen des Isatosaureanhydrids mit Anilen. Monatshefte fur Chemie. 1969. Vol. 100. pages 146-149, especially page 147.	1-15

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance,	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

13 JANUARY 2000

Date of mailing of the international search report

17 MAR 2000

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